TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
C1-A0321P		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/JP2004/018493	10.12.2004	12.12.2003

International Patent Classification (IPC) or national classification and IPC

C12N15/13 , C07K16/46, C12P21/02, 21/08

Applicant

CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/018493

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/018493

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims	1-12	NO
Inventive step (IS)	Claims		YES
	Claims	1-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: WO 01/79494 A1 (Chugai Pharmaceutical Co., Ltd.), 25 October 2001 & AU 2001-46934 A & US 2004/0058393 A1

Document 2: P.J. Hudson and A.A. Kortt, J. Immunol. Methods (1999), Vol. 231, pages 177 to 189

Claims 1 to 12

The invention set forth in claims 1 to 12 lacks novelty in the light of document 1 cited in the international search report.

Document 1 sets forth a single-chain bivalent antibody (sc(FV)2) containing two L chain V regions and two H chain V regions of a monoclonal antibody exhibiting agonist activity by crosslinking cell surface molecules, and indicates that said single chain bivalent antibody has the regions arranged in the sequence [H chain V region]-[L chain V region]-[H chain V region]-[L chain V region], and that these regions are bonded by means of a peptide linker comprising amino acids 1 to 30 (see claims 1 to 3, 5, 13, 17,; page 9, line 22 to page 11, line 7). The MABL-2 antibody sc(Fv)2 prepared in the example of document 1 has a peptide linker comprising amino acid 15 (see page 39, line 11 to page 52, line 22; example 6;

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

fig. 34).

In addition, document 1 sets forth a method wherein a host genetically transformed by a recombinant vector containing DNA which codes said single chain bivalent antibody is cultured, and said single chain bivalent antibody is produced from said culture (see claims 14 to 16; page 5, line 28 to page 6, line 6; page 39, line 11 to page 52, line 22; embodiment 6; fig. 34).

Moreover, document 1 indicates that by modifying an antibody molecule into a single chain bivalent antibody, the molecules on the cell surface are crosslinked, inducing only the desired activity in the cell, and that the modified antibody has a considerably higher activity compared to the original monoclonal antibody. Document 1 also gives thrombopoetin (TPO) as an example of a receptor when the modified antibody is used as an agonist, and indicates that the bivalent single chain Fv to said TPO receptor exhibits higher agonist activity than the agonist activity of human TPO and 12B5IgG (human antibody to human MPL) (see claims 10 and 14 to 16; page 61, lines 6 to 8; page 52, line 23 to page 61, line 8; example 7).

Therefore the invention set forth in claims 1 to 12 of this application is disclosed in document 1.

Claims 1 to 12

The invention set forth in claims 1 to 12 does not involve an inventive step in the light of document 1 cited in the international search report.

Document 1 indicates that the preferred length of a linker peptide for a peptide linker which bonds an H chain V region and an L chain V region varies according

to the receptor which acts as the antigen (see page 10, lines 24 and 25).

In the light of document 1, when producing the single chain bivalent antibody set forth in document 1, determining the appropriate length of the peptide linker according to the target receptor in an attempt to obtain higher agonist activity is a matter which a person skilled in the art could determine as necessary.

Claim 2

The invention set forth in claim 2 does not involve an inventive step in the light of documents 1 and 2 cited in the international search report.

Document 2 sets forth a single chain bivalent antibody having the structure [heavy chain variable region]-[linker]-[light chain variable region]-[linker]-[heavy chain variable region]-[linker]-[light chain variable region](see fig. 2(d)), and indicates that when polymerizing a single chain antibody (scFv), it is possible to design the antibody as an antibody having multiple specificities targeting different antigens (see page 179, left column, lines 12 to 16).

If the "first polypeptide containing the heavy chain variable region and light chain variable region of an antibody" and the "second polypeptide containing the heavy chain variable region and light chain variable region of an antibody" set forth in claim 2 are different, even if different antigens or epitopes are recognized, in the light of document 2, when producing the single chain bivalent antibody set forth in document 1, it would be easy for a person skilled in the art to conceive of having the first polypeptide and the second

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

polypeptide recognize different antigens or epitopes in an attempt to obtain a bispecific antibody.

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, Item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☒ in computer readable form

   c. time of filing/furnishing

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*